Incidence and epidemiology of parapneumonic pleural effusion in children before and during pneumococcal conjugated vaccination era in Belgium (2000-2019)

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Keywords

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Abstract

Background:

Pneumococcal community-acquired pneumonia is frequently complicated by parapneumonic pleural effusion. In Belgium, three pneumococcal conjugate vaccines were introduced between 2007 and 2019. These are successively the heptavalent (PCV7), the 13-valent (PCV13) and the 10-valent (PCV10) pneumococcal conjugate vaccine. Our aim was to assess the effect of pneumococcal conjugate vaccines over time on the incidence of parapneumonic pleural effusion during the pre-vaccination (pre-PCV) and the three vaccination periods.

Methods:

The demographic and clinical-biological characteristics of hospitalized children with pleural effusion complicating community-acquired pneumonia were collected retrospectively between January 2000 and August 2019.

Results:

Among 474 children hospitalized for pneumonia with pleural effusion, Streptococcus pneumoniae was detected in 140 bacteriological samples. During the study period, the overall incidence of parapneumonic pleural effusion increased by 50.8% during the PCV10 period ($p<0.0001$). The incidence of pneumococcal pleural effusion was 27.2‰ during the PCV10 period and increased by approximately 60% compared to the pre-PCV period ($p=0.0005$) with a moderate decrease during the PCV13 period.

Conclusion:

Our study observes an increasing incidence of pleural effusions in children with pneumonia after the introduction of pneumococcal conjugate vaccines in Belgium. The reasons of these increased incidences remain unclear and should be confirmed in larger series of children. Pneumococcal vaccination in children remains however highly recommended by its favorable outcome on overall invasive pneumococcal disease.

Introduction

Community-acquired pneumonia (CAP) is a common pediatric infection and a major source of morbidity and mortality worldwide (1-4). According to data from the World Health Organization, 15% of deaths children under 5 years of age are due to pneumonia (5). In 2017, 808 694 pneumonia-related deaths were recorded in this age group worldwide (5).

Streptococcus pneumoniae (*S. pneumoniae*), is the most common pathogen causing invasive infections such as CAP with bacteremia or empyema, meningitis, osteomyelitis and sepsis (5-8). In 2000, 13.8 million episodes of pneumococcal pneumonia in children under 5 years of age were recorded worldwide (6). Parapneumonic pleural effusion (PPE) complicates nearly half of all pneumococcal pneumonia in some series. It results from microbial invasion and inflammation of the pleural space (9,10). It can progress to empyema corresponding to the accumulation of purulent fluid in the pleural cavity. CAP complicated by PPE or empyema often requires prolonged intravenous antibiotic therapy or even invasive management with percutaneous or surgical chest drainage.

Currently, more than 90 infection-related pneumococcal capsular serotypes have been described (3). Only high incidence invasive pneumococcal diseases (IPD) and antibiotic resistant serotypes are targeted by vaccines (11,12). Before the introduction of the pneumococcal heptavalent conjugate vaccine (PCV7, Prevenar®), 6 to 11 serotypes were predominant in IPD in the different regions of the world (13).

In Belgium, PCV7 was marketed in October 2004 and recommended in the vaccination schedule from January 2007 until September 2011 (Wallonia-Brussels Federation) or July 2011 (Flanders) (11,14). 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar® 13) was then introduced (11). From May 2016 to August 2019 (Wallonia-Brussels) and July 2015 to June 2019 (Flanders), PCV13 was replaced by the 10-valent pneumococcal conjugate vaccine (PCV10, Synflorix®) whose 8 serotypes are conjugated to a non-typable *Haemophilus influenzae* protein D and serotypes 18C and 19F are conjugated to tetanus toxin and diphtheria toxin, respectively (13,15,27). In the other two vaccines (PCV7 and PCV13), serotypes are conjugated to the modified diphtheria toxin (27).

PCV7 coverage includes serotypes 4, 6B, 9V, 14, 18C, 19F, 23F while PCV13 includes six additional serotypes 1, 3, 5, 6A, 7F and 19A (8,11). PCV10 covers PCV7 serotypes and serotypes 1, 5, 7F (13).

Children benefit from a vaccination schedule with 2 doses at 2 and 4 months followed by a booster at 12 months (11).

Many studies carried out in several countries have reported a remarkable decrease in the overall incidence of IPD caused by PCV7

vaccine serotypes (VTs) after its introduction, including pneumonia with pneumococcal bacteremia (2,4,16). But this observation was associated with some "replacement" of the seven VTs by non-vaccine serotypes (NVTs) in IPD (serotypes 1, 3, 5, 6A, 7F and 19A) (3,4,17). Similarly, recent epidemiological data demonstrate an increasing incidence of IPD caused by PCV13 VTs, especially serotypes 19A and 3 during the PCV10 recommendation period which justified the reintroduction of PCV13 vaccination (18,19).

Several studies in pediatric populations have also demonstrated an increasing incidence of pneumococcal empyema before and after PCV7 introduction, potentially associated to such circulating serotypes modifications (8,9,14,20). In contrast, the number of cases decreased after PCV13 introduction (2,8).

Our main objective was to compare the incidence of the demographic, clinical and biological characteristics of pleural effusions before and during the conjugate pneumococcal vaccination era in children in a Belgian pediatric hospital. Our second objective was to describe the evolution of its management.

Methods

Patient enrolment

This study was carried out at Hôpital Universitaire Des Enfants Reine Fabiola in Brussels, a tertiary pediatric hospital of 183 beds.

All children from 0 to 16 years old hospitalized for pneumonia and pleural effusions from January 2000 to August 2019 were identified using the international classification system ICD-9-CM (International Classification of Diseases-9-Clinical Modification) and ICD-10-CM (International Classification of Diseases-10-Clinical Modification). Data were collected retrospectively from their medical files. Demographic, clinical and biological data were encoded for eligible patients during the study period.

Four periods were defined based on vaccine recommendations in Belgium: "pre-PCV" from January 2000 to December 2006, "PCV7" from January 2007 to August 2011, "PCV13" from September 2011 to April 2016, "PCV10" from May 2016 to August 2019.

This study received the approval of the Hôpital Universitaire Des Enfants Reine Fabiola ethics committee (CEH file n° 62/21).

Inclusion criteria and definitions

We included all patients aged 0 to 16 years who were hospitalized for CAP and PPE.

CAP was defined as the association of cough and/or respiratory distress, a body temperature ≥ 38°C and the presence of a pulmonary consolidation on a chest X-ray (21).

PPE was confirmed by a chest X-ray and / or ultrasound.

The diagnosis of pneumococcal CAP was made based on identification of a *S. pneumoniae* by culture and/or polymerase chain reaction in pleural fluid or blood.

Penicillin susceptibility testing was performed on all *S. pneumoniae* isolates recovered. They were classified on report by minimum inhibitory concentration (MIC) as susceptible (MIC ≤ 0.06 µg/mL), intermediate (MIC = 0.12 - 1.0 µg/mL) or resistant (MIC ≥ 2.0 µg/mL) according to CLSI (Clinical and Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing) guidelines.

The serotyping of *S. pneumoniae* was performed using the Quellung reaction capsular typing. Due to a failure to record data, pneumococcal serotypes could be identified only for isolates from patients admitted between January 2005 and August 2019.

Classification of parapneumonic pleural effusions

All ultrasound confirmed pleural effusions were sampled except those less than 10 mm thick (22). We distinguished three PPE categories (simple, complicated and empyema) according to the British Thoracic Society classification based on macroscopic appearance and biochemical and bacteriological characteristics of pleural fluid (9).

Pleural effusions with a macroscopic purulent aspect were considered as "empyema" even in case of negative bacteriological examination. Non-punctured and "unclassifiable" pleural effusions due to lack of information have been classified as "unknown".

Exclusion criteria

We excluded patients with non-parapneumonic pleural effusions, nosocomial pneumonia or in case of missing files. PPE of unknown etiology were not excluded. They were classified as "potential pneumococcal" PPE based on data showing that pneumococcus was the predominant etiological agent recovered in severe and complicated CAP with PPE at the same period in Europe (20).

Patients with more than 1 episode of CAP with PPE and chronic underlying diseases such as heart diseases, chronic respiratory diseases, neurological syndromes, malformative syndromes, hematological and oncological conditions, acquired or congenital immune deficiency or a history of prematurity were not excluded.

Statistics

Data were processed by SAS version 9.4© for Windows. Incidence rates were presented with a 95% confidence interval. Analyzes were performed by vaccination period, year, and age group. Continuous variables are expressed as mean ± standard deviation or median (IQR, interquartile range) and were analyzed by Kruskal-Wallis test. Categorical variables are presented with frequency distributions and were analyzed by Cochran-Armitage trend test. A p-value less than 0.05 was considered statistically significant.

Results

Global epidemiological data

Between January 2000 and August 2019, 6594 children were hospitalized with pneumonia. According to the 4 predefined vaccination periods, the number of cases were respectively: 3057 (January 2000 - December 2006), 1667 (January 2007 - August 2011), 1171 (September 2011 - April 2016) and 699 (May 2016 - August 2019). Vaccination data were not obtained individually but deduced from study periods. At the same period 1143 children were hospitalized with a pleural effusion. Based on the exclusion criteria, 669 cases were excluded (Figure 1). As shown in Figure 1, 474 children presented with a pleural effusion associated with CAP (7.2% of hospitalized pneumonia and 41.5% of pleural effusions all etiologies combined). They were divided into four groups according to the microorganism. A pleural fluid sample was taken from 250 children (52.7%) and a bacteriological pathogen was identified in blood culture and/or pleural fluid culture and/or polymerase chain reaction among 185 cases (39.0%). In 140 cases (29.5%), the microbiological sample revealed *S. pneumoniae*, which allowed them to be classified as CAP with pneumococcal PPE (pPPE). 267 other cases of PPE (56.3%) were classified as potential pneumococcal PPE (ppPPE) due to non-contributive microbiological analyzes.

The demographic, clinical and biological characteristics of the patients are shown in Table 1.

Parapneumonic pleural effusion incidence and characteristics

Between the beginning and the end of the study, the overall incidence of PPE among all hospitalized children with pneumonia increased from 56.3‰ during the pre-vaccination period (172/3057) to 114.4‰ during the 4th period (80/699) with a significant increasing trend of 50.8% ($p<0.0001$). This increase was most pronounced among children between 2 and 5 years old (47.5%; $p<0.0001$) and in males (49.4%; $p<0.0001$).

The pPPE incidence significantly increased, from 11.4‰ in the pre-

PCV period to 27.2‰ in the PCV10 period (p=0.0005). This represents a nearly 60% increase in CAP with PPE due to *S. pneumoniae*, especially in children 2 to 5 years old (p = 0.0003). This upward trend in pPPE is significant in both genders (female, p=0.01; male, p=0.02). The ppPPE also significantly increased, but in a lesser proportion (by 50.1%) with an incidence going from 35.0‰ to 70.1‰ (p<0.0001) between pre-PCV and PCV10 periods. Detailed data are available in Table 2 and Figure 2.

Among pPPE, complicated PPE had a significant upward trend (+ 81.3%) to reach a proportion of 47.4% of all PPE during the PCV10 period (95% CI, 5.6-58.7; p=0.001). On the contrary a significant decrease in empyema was observed among all PPE (-41.4%; p=0.03) and among pPPE (-64.8%; p=0.003). Detailed data are available in Table 3.

Parapneumonic pleural effusion treatment and short-term morbidity

The use of antibiotic therapy alone in the management of CAP complicated by PPE significantly increased by more than 30% throughout the study period (p=0.0002). The duration of intravenous antibiotic therapy significantly decreased with a median duration going from 14 to 7 days for total PPE and from 12 to 5 days for ppPPE (p<0.0001; p<0.0001). The decrease in intravenous antibiotic therapy duration for pPPE was not statistically significant, going from a median duration of 20 to 14 days between the pre-PCV and PCV10 periods (p=0.45). The use of thoracic drainage (percutaneous or surgical) decreased by 40.6% and 74.9% for total PPE (p=0.0004) and ppPPE (p<0.0001) respectively with a significant decrease in the duration of drainage (p<0.0001; p=0.02). However, a non-significant increase in thoracic surgery (VATS, video-assisted thoracoscopic surgery) was observed for pPPE (p=0.12).

The incidence of pulmonary complications varied over time with a non-significant decreasing trend for pPPE (p=0.64). A decreasing trend in pulmonary complications was found to be significant for ppPPE (p<0.0001) and for total PPE (p<0.0001) with reduction of pneumatoceles and pachypleuritis (Table 3).

Pneumococcal serotypes

Pneumococcal serotyping was obtained for 49 bacteriological samples isolated between 2005 and 2019. Except for two isolates, the serotypes identified were all VTs included in PCV13, in particular serotypes 1, 3, 5, 7F, 19A. There were 26 cases attributed to serotype 1, 2 cases to serotype 3, 7 cases to serotype 5, 1 case to serotype 7F, 1 case to serotype 8, 1 case to serotype 12F and 11 cases to serotype 19A. The serotypes distribution by vaccination period is shown in Table 4. Serotypes 1 and 19A were the most frequently found and represented approximately 75% of our identified cases (37 of 49 samples). PCV13 VTs were predominant during the PCV7 period. They decreased during the PCV13 period. Then, during the PCV10 period, serotype 19A increased slightly again and we observed cases due to serotypes 3, 8 and 12F. Among 10 patients admitted during the PCV13 period from whom serotypes were identified, 8 children had received three doses of PCV7 and 2 children had not been vaccinated against pneumococci. Among 6 patients in the PCV10 period, 3 children had received three doses of PCV13 and the other 3 children had received PCV10, one of whom had received only two doses. Serotype 1 was predominant during the first three periods and its incidence decreased to disappear during the PCV10 period (p=0.12) (Table 4). Serotypes 8 and 12F are not included in the VTs. The two patients from whom these serotypes were isolated had received a complete schedule of PCV13 vaccination.

S. pneumoniae identification and penicillin susceptibility

There was a significant increase in the use of polymerase chain reaction on pleural fluid as diagnostic tool for etiology of the PPE between the pre-PCV and PCV10 periods (0% to 57.9%; p<0.0001) (Table 4). The strains of *S. pneumoniae* isolated in culture and for which antibiotic susceptibility could be determined remained predominantly susceptible to first-line antibiotics during the vaccination periods (Table 5). Penicillin-resistant *S. pneumoniae* was identified in 3 children. All were 19A serotypes. Among the 3 patients, 1 had a penicillin allergy and was treated immediately with ciprofloxacin, 1 had a penicillin-resistant strain with an MIC of 1 µg/ml and was treated with high-dose penicillin and 1 died before receiving the antibiotic susceptibility profile.

Discussion

To assess the impact of pneumococcal vaccination on the occurrence of PPE, we performed a 20-year single-center retrospective study at Hôpital Universitaire Des Enfants Reine Fabiola, a tertiary pediatric hospital in Brussels. Our study suggests that the overall incidence of PPE among hospitalized children with CAP increased by 50.8% in 2019 compared to the pre-vaccination period.

This increase is primarily induced by the increased incidence of proven and potential pneumococcal PPE during vaccination periods. Moreover, we observe an increase of more than 50% in the incidence of the pneumococcal PPE after the introduction of pneumococcal vaccination, mainly in children under 5 years of age and in the category of complicated PPE. Nevertheless, based on short-term pulmonary complications, need for surgery and antibiotic duration the severity of pneumococcal PPE does not seem to vary over the different periods. This observation could be related with the decrease of the most aggressive serotypes by vaccination. To our knowledge, there is no study that has specifically evaluated the evolution of the number of PPE during the three pneumococcal vaccines periods even though reports of increased incidence of pneumococcal PPE before and following the introduction of PCV7 vaccine have already been published (8,23,12). The upward trend in the incidence of pneumococcal PPE before and after the PCV7 introduction in the vaccination schedule is also objectified in our study. This observation may be the consequence of a majority of complicated CAP related to non-PCV7 serotypes, notably 1, 3, 5, 7F and 19A (12). In addition, a study of serotype distribution in pediatric CAP showed that CAP associated with PCV7 serotypes are rare in PCV7 vaccinated children (21).

The consequences pneumococcal vaccines on the development of IPD in general have been widely analyzed in pediatric and adult populations around the world (15,24-26). Several recent studies show a decrease in the overall incidence of IPD after the introduction of PCV10 and PCV13 (24-26). On the contrary, a Belgian national retrospective observational study by Desmet et al. showed a pronounced upward trend in the incidence of IPD in children under 2 years of age after the replacement of the PCV13 by PCV10 between the years 2017 and 2018 (15). In Belgium, an increased rate of PCV13 non-PCV10 VTs has been identified in IPD in children after the introduction of PCV10 (15,27). Consequently, the national recommendation of pneumococcal vaccination has been modified towards PCV13 and a catch-up vaccination with PCV13 has been recommended for the patient with immunocompromising conditions at risk of IPD (18,27).

The World Health Organization recommends either a 2+1 schedule with 2 primary doses and a booster between 9 and 12 months of age or a 3+0 schedule with 3 primary doses without a booster (28). Currently, there is no consensus on the optimal regimen (28). In Belgium, we apply the 2+1 schedule based on the opinion of the Superior Health Council (27). The booster has been shown to induce a longer and more effective immunogenicity against some serotype such as serotype 1 (28).

At the worldwide level, studies have shown how complex the relation is between pneumococcal vaccine formulation and IPD epidemiology (2,8,15,23-27,29).

Our serotyping data are too scarce for complete analyses of serotypes distribution but overall concordant with several studies showing that serotype 1 is the most prevalent in CAP and empyema in children

(7,11). During the PCV10 period, we also observed a re-emergence of PCV13 non PCV10 VTs as reported in the Belgian national study by Desmet et al. (15). But we have limited serotype data which makes difficult to conclude on the benefit of a catch-up vaccination and on the impact of a booster vaccination schedule [2+1].

Our study is subject to several limitations. The retrospective nature of the study is associated with the unavailability of some data. We recruited our patients using the international classification of diseases encoding system which remains imprecise. However, the analysis of all records was performed by a single author to eliminate interobserver variability in data encoding. It should be noted that a change in the management of pneumonia took place since 2008 at our hospital and resulted in shorter intravenous antibiotic treatment durations and in more frequent outpatient treatments with oral antibiotics. This could have affected the proportion of PPE among all hospitalized CAP since the presence of a PPE was considered a reason for hospitalization. This change also makes that the duration of intravenous antibiotics is an unreliable parameter to assess the severity of the infection. Likewise, the incidence of chest drainages is prone to overestimation due to inter-hospital transfers to our tertiary center for patients with an indication for chest tube placement. Our results can also be influenced by the use of polymerase chain reaction which has a greater sensitivity than conventional methods (culture of biological fluid) (30,31). It may partly explain the increase in the incidence of proven pneumococcal PPE, but is however not sufficient to explain the increase in the incidence of potential pneumococcal PPE. CAP without PPE were not considered, therefore our observations cannot be extrapolated to the general population of CAP.

Conclusion

Although the overall incidence of empyema remains low, our data suggest a significant increase in the incidence of PPE during vaccine periods compared to the pre-vaccination period. A moderate reduction of the incidence of pPPE was observed during the PCV13 period. But after the transition to PCV10 we observed an increased incidence of total PPE. The epidemiology of pPPE is influenced by multiple factors which makes it difficult to interpret the outcomes. Currently, it is recommended to continue pneumococcal vaccination with PCV13 based on evidence of decreasing IPD in children. However reporting programs such as Pedisurv in Belgium and national and international surveys remains crucial to understand the dynamics of the pPPE incidence in the future.

Disclosure of conflicts of interest

The authors have no conflict of interest to declare.

Table 1: Clinical, biological and demographic characteristics of patients

Variables	Total PPE (n = 474)	Pneumococcal PPE (n = 140)	Potential pneumococcal PPE (n = 267)
Age (month), median (IQR)	41 (22-68)	37 (23-60)	48 (24-72)
Age (groups), n (%)			
< 2 years old	80 (16.9)	25 (17.9)	34 (12.7)
2 – 5 years old	223 (47.0)	74 (53.6)	123 (46.1)
≥ 5 years old	171 (36.1)	41 (29.3)	110 (41.2)
Male sex, n (%)	264 (55.7)	75 (53.6)	156 (58.4)
Pneumococcal vaccination status, n (%)			
No vaccine	216 (45.6)	52(37.1)	132 (49.4)
PCV7	133 (28.1)	57 (40.7)	63 (23.6)
PCV13	64 (13.5)	18 (12.9)	36 (13.5)
PCV10	24 (5.1)	7 (5.0)	12 (4.5)
Unknown	37 (7.8)	6 (4.3)	24 (9.0)
Prematurity, n (%)	25 (5.3)	7 (5.0)	13 (4.9)
Antecedent of lower respiratory tract infection, n (%)	99 (20.9)	18 (12.9)	71 (26.6)
IPD risk factors, n (%)	65 (13.7)	11 (7.9)	45 (16.9)
Asthma, n (%)	16 (3.4)	4 (2.9)	12 (4.5)
Hemoglobinopathy, n (%)	22 (4.6)	2 (1.4)	17 (6.4)
Immunodeficiency, n (%)	8 (1.7)	0 (0)	7 (2.6)
Malformative syndrome, n (%)	9 (1.9)	3 (2.1)	5 (1.9)
Neurological disease, n (%)	9 (1.9)	2 (1.4)	4 (1.5)
Oncological condition, n (%)	6 (1.3)	1 (0.7)	3 (1.1)

Table 2: Evolution of the incidence of parapneumonic pleural effusions (n) among hospitalized patients with pneumonia (N) during vaccination periods

	Total PPE total (n = 474)						Pneumococcal PPE (n = 140)						Potential pneumococcal PPE (n = 267)					
	Periods						Periods						Periods					
Variables, n (% pneumonia)	Pre-PCV (N = 2057)	PCV7 (N = 1667)	PCV13 (N = 1171)	PCV10 (N = 699)	Difference between pre-PCV and PCV10, %	p [a]	Pre-PCV (N = 2057)	PCV7 (N = 1667)	PCV13 (N = 1171)	PCV10 (N = 699)	Difference between pre-PCV and PCV10, %	p [a]	Pre-PCV (N = 2057)	PCV7 (N = 1667)	PCV13 (N = 1171)	PCV10 (N = 699)	Difference between pre-PCV and PCV10, %	p [a]
Total PPE	172 (56.3)	121 (72.6)	101 (86.3)	80 (114.4)	+ 50.8	<0.0001	-	-	-	-	-	-	-	-	-	-	-	-
Microbial agent																		
Pneumococcal PPE	35 (11.4)	57 (34.2)	29 (24.8)	19 (27.2)	+ 58.1	0.0005	-	-	-	-	-	-	-	-	-	-	-	-
Potential pneumococcal PPE	107 (35.0)	53 (31.8)	58 (49.5)	49 (70.1)	+ 50.1	<0.0001	-	-	-	-	-	-	-	-	-	-	-	-
Bacterial PPE *	22 (7.2)	9 (5.4)	8 (6.8)	6 (8.6)	+ 16.3	0.88	-	-	-	-	-	-	-	-	-	-	-	-
Viral PPE	8 (2.6)	2 (1.2)	6 (5.1)	6 (8.6)	+ 69.8	0.02	-	-	-	-	-	-	-	-	-	-	-	-
Age groups																		
< 2 years old	29 (9.5)	18 (10.8)	10 (8.5)	23 (32.9)	+ 71.1	0.0004	7 (2.3)	9 (5.4)	3 (2.6)	6 (8.6)	+ 73.3	0.06	13 (4.3)	7 (4.2)	4 (3.4)	10 (14.3)	+ 69.9	0.02
2 à 5 years old	78 (25.5)	55 (33.0)	56 (47.8)	34 (48.6)	+ 47.5	<0.0001	16 (5.2)	26 (15.6)	21 (17.9)	11 (15.7)	+ 66.9	0.0003	53 (17.3)	24 (14.4)	27 (23.1)	19 (27.2)	+ 36.4	0.06
≥ 5 years old	65 (21.3)	48 (28.8)	35 (29.9)	23 (32.9)	+ 35.3	0.03	12 (3.9)	22 (13.2)	5 (4.3)	2 (2.9)	- 25.6	1.00	41 (13.4)	22 (13.2)	27 (23.1)	20 (28.6)	+ 53.1	0.002
Sex																		
Female	77 (25.2)	53 (31.8)	43 (36.7)	37 (52.9)	+ 52.4	0.0002	14 (4.6)	29 (17.4)	13 (11.1)	9 (12.9)	+ 64.3	0.01	66 (21.6)	36 (21.6)	37 (31.6)	25 (35.8)	+ 39.7	0.04
Male	95 (31.1)	68 (40.8)	58 (49.5)	43 (61.5)	+ 49.4	<0.0001	21 (6.9)	28 (16.8)	16 (13.7)	10 (14.3)	+ 51.7	0.02	49 (16.0)	19 (11.4)	23 (19.6)	20 (28.6)	+ 44.1	0.0003

a Cochran-Armitage test for trend; p, p-value; n, number of parapneumonic pleural effusion cases; N, number of hospitalized cases with pneumoniae per vaccination period.

* Other than pneumococcus

Table 3: PPE characteristics and management

	Total PPE (n = 474)						Pneumococcal PPE (n = 140)						Potential pneumococcal PPE (n = 267)					
	Periods						Periods						Periods					
Variables, n (% PPE)	Pre-PCV (n = 172)	PCV7 (n = 121)	PCV13 (n = 101)	PCV10 (n = 80)	Difference between pre-PCV and PCV10, %	p a	Pre-PCV (n = 35)	PCV7 (n = 57)	PCV13 (n = 29)	PCV10 (n = 19)	Difference between pre-PCV and PCV10, %	p a	Pre-PCV (n = 107)	PCV7 (n = 58)	PCV13 (n = 58)	PCV10 (n = 49)	Difference between pre-PCV and PCV10, %	p a
Variables, n (% PPE)																		
PPE categories																		
Unknown	93 (54.1)	48 (39.7)	63 (62.4)	52 (65.0)	+ 16.8	0.03	10 (28.6)	10 (17.5)	4 (13.8)	5 (26.3)	- 8.0	0.60	67 (62.6)	37 (69.8)	52 (89.7)	41 (83.7)	+ 25.2	0.0002
Simple	11 (6.4)	6 (5.5)	5 (5.0)	4 (5.0)	- 21.9	0.64	1 (2.9)	0 (0)	3 (10.3)	1 (5.3)	+ 45.3	0.25	9 (8.4)	3 (5.7)	1 (1.7)	3 (6.1)	- 27.4	0.32
Complicated	24 (14.0)	33 (27.3)	15 (14.9)	12 (15.0)	+ 6.7	0.96	3 (8.6)	17 (29.8)	11 (37.9)	9 (47.4)	+ 81.3	0.001	19 (17.8)	11 (20.8)	3 (5.2)	0 (0)	- 100	0.0003
Empyema	44 (25.6)	36 (29.8)	18 (17.8)	12 (15.0)	- 41.4	0.03	21 (60.0)	30 (52.6)	11 (37.9)	4 (21.1)	- 64.8	0.003	12 (11.2)	2 (3.8)	2 (3.4)	5 (10.2)	- 8.9	0.49
Treatment																		
Antibiotic alone	70 (40.7)	45 (37.2)	56 (55.4)	50 (62.5)	+ 34.9	0.0002	8 (22.9)	8 (14.0)	1 (3.4)	3 (15.8)	- 31.0	0.18	49 (45.8)	36 (67.9)	48 (82.8)	41 (83.7)	+ 45.3	0.0001
Single or repeated thoracocentesis	8 (4.7)	1 (0.8)	1 (1.0)	4 (5.0)	+ 6.0	0.71	1 (2.9)	0 (0)	0 (0)	0 (0)	- 100	0.39	6 (5.6)	0 (0)	0 (0)	2 (4.1)	- 26.8	0.36
Percutaneous chest tube	57 (33.1)	37 (30.6)	19 (18.8)	10 (12.5)	- 62.2	<0.0001	13 (37.1)	23 (40.4)	8 (27.6)	7 (36.8)	- 0.8	0.65	33 (30.8)	10 (18.9)	6 (10.3)	2 (4.1)	- 86.7	<0.0001
Surgery (VATS)	37 (21.5)	38 (31.4)	25 (24.8)	16 (20.0)	- 7.0	0.88	13 (37.1)	26 (45.6)	20 (69.0)	9 (47.4)	+ 21.7	0.12	19 (17.8)	7 (13.2)	4 (6.9)	4 (8.2)	- 53.9	0.04
Pulmonary complications	57 (33.1)	20 (16.5)	18 (17.8)	7 (8.8)	- 73.4	<0.0001	14 (40.0)	12 (21.1)	12 (41.4)	5 (26.3)	- 34.3	0.64	31 (29.0)	5 (9.4)	3 (5.2)	0 (0)	- 100	<0.0001
Pneumothorax	15 (8.7)	12 (9.9)	13 (12.9)	3 (3.8)	- 56.3	0.56	5 (14.3)	7 (12.3)	9 (31.0)	3 (15.8)	+ 9.5	0.30	7 (6.5)	3 (5.7)	2 (3.4)	0 (0)	- 100	0.07
Pneumatocele	18 (10.5)	8 (6.6)	3 (3.0)	4 (5.0)	- 52.4	0.03	4 (11.4)	5 (8.8)	3 (10.3)	3 (15.8)	+ 27.8	0.68	10 (9.3)	3 (5.7)	0 (0)	0 (0)	- 100	0.002
Pachypleuritis	26 (15.1)	6 (5.0)	3 (3.0)	0 (0)	- 100	<0.0001	6 (17.1)	5 (8.8)	1 (3.4)	0 (0)	- 100	0.02	15 (14.0)	1 (1.9)	1 (1.7)	0 (0)	- 100	0.0001
Lung abscess	9 (5.2)	4 (3.3)	1 (1.0)	3 (3.8)	- 26.9	0.26	4 (11.4)	3 (5.3)	1 (3.4)	2 (10.5)	- 7.9	0.74	4 (3.7)	0 (0)	0 (0)	0 (0)	- 100	0.04
Variables, median, day (IQR)						p b						p b						p b
Total length of stay	15 (9 – 20)	13 (7 – 18)	10 (5 – 16)	9 (4 – 16)	-	<0.0001	19 (13 – 23)	16 (13 – 19)	17 (13 – 28)	18 (12 – 22)	-	0.24	13 (8 – 19)	9 (5 – 14)	6 (4 – 11)	5 (3 – 12)	-	<0.0001
Duration of intravenous antibiotic therapy	14 (7 – 20)	14 (6- 18)	8 (4 – 14)	7 (3 – 14)	-	<0.0001	20 (15 – 21)	16 (13 – 19)	14 (12 – 23)	14 (10 – 19)	-	0.45	12 (7 – 17)	8 (5 – 14)	5 (3 – 8)	5 (2 – 10)	-	<0.0001

a Cochran-Armitage test for trend

b Kruskal-Wallis test

p, p-value; n, number of parapneumonic pleural effusion cases

Table 4: Evolution of identification methods and pneumococcal serotypes during vaccination periods

Variables, n (% pneumococcal PPE)	Periods				Difference between pre-PCV and PCV10, %	p *
	Pre-PCV (n = 35)	PCV7 (n = 57)	PCV13 (n = 29)	PCV10 (n = 19)		
Identification of *S. pneumoniae*						
Blood culture	25 (71.4)	24 (42.1)	9 (31.0)	4 (21.0)	- 70.6	0.0001
Pleural fluid culture	8 (7.4)	5 (8.8)	3 (10.3)	3 (15.8)	+ 53.2	0.40
Blood and pleural fluid culture	2 (5.7)	5 (8.8)	2 (6.9)	1 (5.3)	- 7.0	0.92
Polymerase Chain Reaction	0 (0)	23 (40.3)	15 (51.7)	11 (57.9)	+ 100	<0.0001
Serotypes						
1	8 (22.9)	11 (19.3)	7 (24.1)	0 (0)	- 100	0.12
3	0 (0)	0 (0)	0 (0)	2 (10.5)	+ 100	0.01
5	1 (2.9)	4 (7.0)	2 (6.9)	0 (0)	- 100	0.81
7F	0 (0)	1 (1.7)	0 (0)	0 (0)	-	0.81
8	0 (0)	0 (0)	0 (0)	1 (5.3)	+ 100	0.26
12F	0 (0)	0 (0)	0 (0)	1 (5.3)	+ 100	0.07
19A	2 (5.7)	6 (10.5)	1 (3.4)	2 (10.5)	+ 45.7	0.88
No serotypes	24 (68.6)	35 (61.4)	19 (65.5)	13 (68.4)	- 0.3	0.94

a Cochran-Armitage test for trend; p, p-value; n, number of pneumococcal parapneumonic pleural effusion cases.

Table 5: Evolution of identification methods and pneumococcal serotypes during vaccination periods

Variable, n (% pneumococcal PPE)	Periods			
	Pre-PCV (n = 35)	PCV7 (n = 57)	PCV13 (n = 29)	PCV10 (n = 19)
Penicillin susceptibility				
Susceptible	28 (80.0)	29 (50.9)	12 (41.4)	8 (42.1)
Intermediate	5 (14.3)	3 (5.3)	0 (0)	0 (0)
Resistant	0 (0)	2 (3.5)	1 (3.4)	0 (0)

n, number of pneumococcal parapneumonic pleural effusion cases

Figure 2: Evolution of the annual incidence of parapneumonic pleural effusions

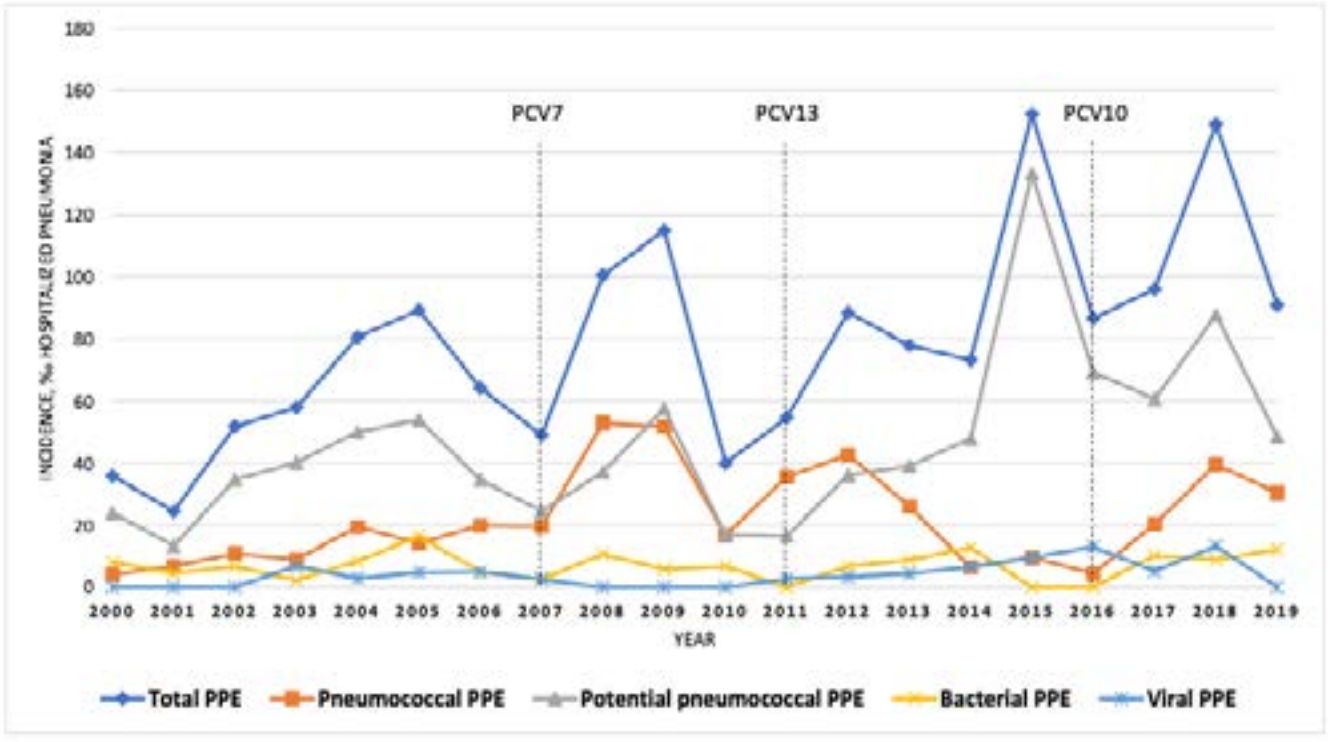
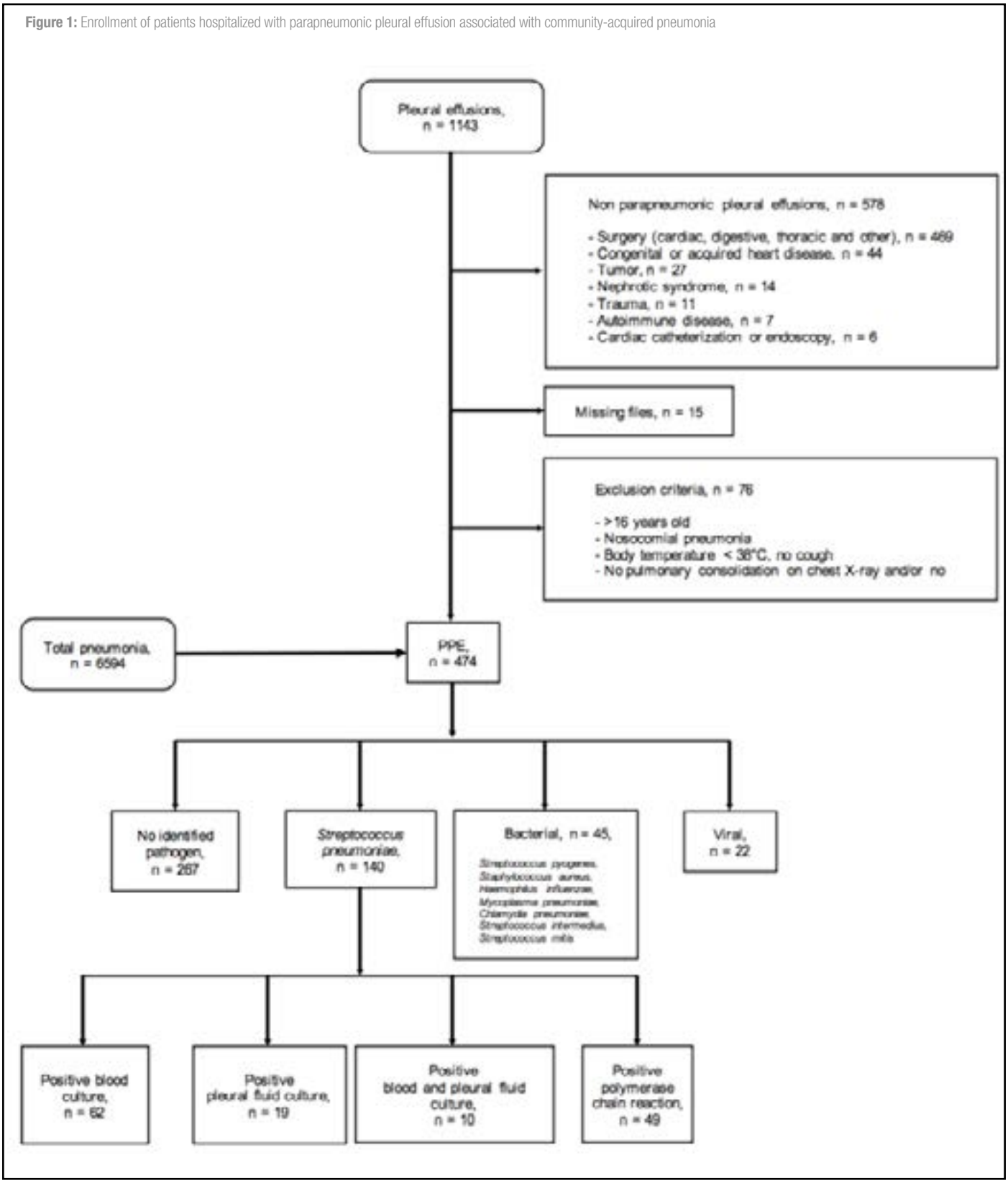


Figure 1: Enrollment of patients hospitalized with parapneumonic pleural effusion associated with community-acquired pneumonia



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